Chapter 5. Reproductive Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and reproduction from the 1997 OEHHA report and this update are provided below in Table 5.0. The conclusions are based on a weight of evidence approach. In summary, there is evidence suggestive of an association between ETS exposure and fertility and menstural cycle disorders.

Table 5.0 ETS and Reproduction: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
Fertility or fecundability	8	5	Inconclusive	Suggestive
Lower age at Menopause	2	1	Inconclusive	Inconclusive
Menstrual cycle Disorders	0	3	Inconclusive	Suggestive
Male reproductive dysfunction	0	1	Inconclusive	Inconclusive

5.0. Introduction

The study of reproductive toxicity includes measures of: female fertility and fecundability; other female reproductive effects, such as lowered age at menopause and menstrual disorders; and male reproductive effects, including altered sperm parameters, which may influence a couple's fertility and/or fecundability. Very few studies prior to the Office of Environmental Health Hazard Assessment (OEHHA) 1997 review (Cal/EPA, 1997; National Cancer Institute 1999) or since then have investigated the effects of ETS exposure on male and female reproductive function. Of these, most have examined delay to conception in women who eventually achieve pregnancy as an indication of sub-fecundability. Many of these studies were designed to look at the woman's active smoking, not ETS exposure, but also reported the husband's smoking status, a surrogate for ETS exposure used in studies of other outcomes. Three of the studies reviewed for the 1997 report and one published since then (Table 5.1) examined the possibility of an effect on women's fertility occurring earlier in development by trying to ascertain childhood and *in utero* exposure to ETS. Unlike the 1997 review, this report also includes two studies of the

effect of ETS on pregnancy rates in women enrolled in assisted reproductive technology programs such as in-vitro fertilization and gamete intrafallopian transfer (GIFT).

The discussion below of the potential impact of ETS on each outcome begins with a brief review of epidemiological studies that assessed the effect of active smoking. Although reviewing active smoking effects is not the purpose of this document, the review of these studies is to provide a context within which to consider the results of the studies of ETS exposure. Epidemiologic studies of ETS exposure are discussed in more detail, followed by a description of pertinent animal studies. Studies are then discussed as a group and conclusions are presented.

5.1. Female Fertility and Fecundability

In epidemiological studies, measurement of female fertility (ability to reproduce, as measured by actual live births) and fecundability (the probability of conceiving in a given menstrual cycle) generally relies on reported failure to conceive or delay to conception following a time period of unprotected sexual intercourse. Infertility is commonly defined as not becoming pregnant within a year of unprotected intercourse; of course, some couples may go on to conceive later. Fecundability may be measured by determining the number of cycles needed to conceive and calculating the conception rate in each cycle. The probabilities (or rates) of conception can then be compared between two groups – exposed and unexposed – in the form of a ratio. When such a "fecundability ratio" (FR) is less than one, it indicates that the exposed group has lower or "sub"-fecundability than the comparison group. When examining fertility and fecundability, covariates related to sexual practices are important to consider, including frequency and timing of coitus relative to ovulation, contraceptive use, and history of sexually transmitted diseases, as well as maternal age, socioeconomic status and reproductive history. In animal studies, measures of female fertility derived from the standard multigeneration study in rodents are the fertility index, the fecundity index, the mating index and the parturition index; prior to 1997 multigeneration studies had not been conducted with tobacco smoke. However, a newer study is reviewed in this report. Reproductive organ weights and histology, ovulation, estrus cycles, mating behavior, implantation and resorption may be directly determined from other study designs, and effects on these parameters are considered relevant to female fertility.

5.1.1. Findings on Human Studies of Female Fertility and Fecundability and Active Smoking from the 1997 OEHHA Report

The following finding was included in the 1997 report:

"Active smoking by women has been found to be associated with decreased fertility in a number of studies (reviewed in Stillman *et al.*, 1986; Spira *et al.*, 1987; Westhoff, 1990). Associations have been found between smoking and both delay to conception and infertility, particularly related to tubal factors. Delay to conception has been measured in different time intervals, but studies have found increased risks of 40-80 percent among smokers (*e.g.*, odds ratios of 1.4-1.8) (Howe *et al.*, 1985). The studies which found an association with tubal infertility reported odds ratios of 1.6-3.3 (Daling *et al.*, 1986; Stillman *et al.*, 1986). Many of the studies have found a dose-response effect. The 1980 Surgeon General's report (U.S. Department of Health and Human Services, 1980) stated that 'cigarette smoking appears to exert an adverse effect on fertility' and many of the important studies were conducted since that report was published."

5.1.2. Human Studies of Female Fertility and Fecundability and ETS Exposure

5.1.2.1. Summary of previous findings

The 1997 report reviewed three studies that examined conception delays (in women who eventually became pregnant) with respect to spousal smoking habits. Two of the studies (Suonio *et al.*, 1990; Olsen, 1991), both conducted in Scandinavia, found significantly increased risks (about 30%) of conception delays (of six to twelve months). This approaches the magnitude of increased risk reported for active smoking by Suonio *et al.* (1990) (50%) and by Olsen (1991) (67% to 89%). A study in the United States did not find such an association (Baird and Wilcox, 1985), nor did a study of time to conception in Dutch women (Florack *et al.*, 1994). The U.S. study had more information about sexual practices and evaluated delay to conception in a more rigorous fashion than did either of the positive Scandinavian studies. In addition, because ETS exposure was defined as spousal smoking in these studies, the association seen may have been due to direct effects on male reproductive parameters. The authors of the report concluded that it was not possible to determine from the studies conducted to date whether ETS exposure as an adult is associated with female fertility.

The 1997 report also reviewed three studies which examined childhood ETS exposure and fecundability (Wilcox *et al.*, 1989; Weinberg *et al.*, 1989; Schwingl, 1992). Two of them, conducted by the same investigators but in different populations, found that childhood exposure was associated with a statistically significant increase in the fecundability ratio, or likelihood of conceiving; the third study did not confirm this finding. No mechanism to explain this increased fecundability has been suggested by the data collected to date. The 1997 report concluded that the data were inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability.

5.1.2.2. Newer Epidemiologic Data

Table 5.1 ETS Exposure and infertility or fecundability: Adult and in-utero Exposure

Authors (yr) Location	Design (study size)	Exposure Definition/Measure	Results[1]	Comments
Sterzik *et al.* (1996) United States	Prospective study of women attending an in-vitro fertiliz-ation program (n=197)	Cotinine concentration in follicular fluid.	No difference in fertilization or pregnancy rates among nonsmokers, passive smokers and smokers.	No adjustment for confounders.
Bolumar *et al.* (1996) Several European countries	Retrospective interview of pregnant volunteers (n = 2,587). Population-based sample of women who had planned a pregnancy (n=3,553)	Husband smoking	No association of male smoking with delay to conception (> 9.5 months) after adjustment for confounders.	Large sample size and control for several confounders, including frequency of sexual intercourse. Prospective analysis in a population based sample. Husband's smoking only asked as yes/no.
Chung *et al.* (1997) United States (Florida)	Prospective study of women undergoing gamete intrafallopian transfer (GIFT). (n=98)	Any household member smoking, including husband	No difference in pregnancy rates between passive smokers and nonsmokers. Live birth rates were 23.1% in passive smokers and 33.3% in nonsmokers. This difference was not statistically significant ($p > 0.05$).	Small sample size (only 13 passive smokers), limited power to detect effect. Looked at possibly confounding variables such as age and diagnosis, but did not adjust for these. Pregnancy and live birth rates significantly lower in active smokers.
Jensen *et al.* (1998) Denmark	Prospective study of couples planning a pregnancy, followed for 6 menstrual cycles or until pregnant (n = 430)	Husband smoking, exposure *in utero* and during childhood	FR = 0.70 (0.48-1.03) for nonsmoking women exposed *in utero*. Present smoking in husbands exposed *in utero* reduced FR to 0.83 (0.53-1.30), but was not statistically significant.	Eliminated cycles where no intercourse occurred during ovulation period. Controlled for BMI, alcohol intake, and reproductive diseases.
Hull *et al.* (2000) United Kingdom	Retrospective study of pregnant women (n=8,559)	Partner or other household members smoking. Exposure to cigarette smoke at work	OR of delay to conception > 6 months for passive exposure only, at home or at work = 1.17 (1.02-1.37). OR of delay to conception >12 months for passive exposure only, at home or at work =1.14 (0.92-1.42)	Adjusted for several important confounders.

[1]OR = odds ratio:, BMI = Body Mass Index , FR = fecundability ratio, which indicates probability of conception at each cycle. FR >1 indicates improved fecundability, whereas FR <1 indicates sub-fecundability, when comparing 2 groups

Bolumar et al., 1996. This study examined the effect of female and male smoking on time to pregnancy in a very large sample of couples from several European countries. Smoking by the male partners was the only measure of passive smoke exposure for the women. Two types of samples were used: population-based samples of women aged 25-44 randomly selected from census registers and electoral rolls who had a planned pregnancy in the past and/or had been attempting to conceive more than 9.5 months prior to interview and were not pregnant (n=3,553); and samples of pregnant women (at least 20 weeks pregnant) who had planned their pregnancies and were recruited during prenatal visits (n=2,587). The outcome studied was subfecundity, defined as time to pregnancy > 9.5 months. Data on smoking were obtained for the time when the women started trying to become pregnant. Women were asked the number of cigarettes they usually smoked per day, and the male partners were only asked whether or not they smoked at this time. In addition to the smoking data, the authors collected data on the following potential confounders: mother's education, paid work, age, parity, alcohol and coffee consumption, use of oral contraceptives within 12 months prior to the starting time, and frequency of sexual intercourse.

The authors found a strong association between female smoking of more than half a pack of cigarettes per day and subfecundity in the population sample for both the first planned pregnancy (adjusted OR=1.7, 95% CI 1.3-2.1) and the most recent attempt to become pregnant (adjusted OR=1.6, 95% CI 1.3-2.1). Similar results were seen in the women recruited during their prenatal visits (adjusted OR=1.7, 95% CI 1.3-2.3). However, no significant association was seen with male smoking in the population sample, (OR=0.9, 95% CI 0.1-1.1, first pregnancy and OR=1.0, 95% CI 0.9-1.3, most recent attempt to become pregnant); or in the prenatal visit sample (OR=0.9, 95% CI 0.7-1.1).

This study had several strengths. First, it included a large population based sample from several countries and found consistent results across countries. Second, it collected smoking data at the time of the start of the waiting period. Third, it included several important confounders in the analysis such as past use of oral contraceptives and frequency, but not timing, of sexual intercourse. The main limitation of this study was the data on passive exposure, which was indicated only by smoking (yes/no) in the male partner. The failure to find an effect of male smoking may have been due to the imprecise measure of cigarette smoke

exposure. The Hull (2000) study found an effect of male smoking only for the highest category of smoking.

Sterzik et al., 1996. The purpose of this study was to look at the association between cotinine concentration in follicular fluid (FF) recovered by follicle aspiration and the fertilization and pregnancy rates in an in vitro fertilization (IVF) program. Cotinine, the main metabolite of nicotine, has a half-life of 16 to 20 hours, and correlates well with the total amount of inhaled cigarette smoke. A total of 197 patients (age range 23 to 39 years) were recruited into the study. Entry criteria were a pathological tubal factor as the cause of sterility, normal spermiogram in the male partner, duration of sterility > 1 year, and positive follicle aspiration after hormonal stimulation. Patients were treated with human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG) for follicle stimulation and induction of ovulation. The authors assessed history of smoking with a questionnaire but used FF cotinine concentrations to classify women as non-smokers ($\leq$ 20 ng/mL, n = 68); passive smokers (> 20 ng/mL and $\leq$ 50 ng/mL, n = 26); and active smokers (> 50 ng/mL, n = 103), based on a German study of active and passive smoking in pregnancy and serum cotinine levels (Grab *et al.*, 1988). The authors stated that FF cotinine concentrations correlate well with serum concentrations. Fertilization was diagnosed 18 to 24 hours after insemination when two pronuclei were visible. Pregnancy was defined by sonographic detection of positive fetal heart movement $\geq$ 28 days after embryo transfer. The fertilization rate per cycle was 67.6% for nonsmokers, 57.7% for passive smokers, and 67.9% for active smokers. The pregnancy rates were 32.6%, 33.3%, and 32.9%, respectively. None of these differences were statistically significant. However, the authors found a significant difference between active smokers and nonsmokers ($P < 0.025$) for serum concentration of estradiol (E_2), the primary estrogen produced by the ovaries. Between passive and nonsmokers, no significant E_2 level differences were found. Overall a negative correlation was found between cotinine and E_2 values for all patients ($r = -.065$, $P < 0.01$).

The authors concluded that the absence of association between active, passive and nonsmoking and the rates of fertilization and pregnancy in women attending an IVF program was valid only for the specific cohort of patients who were young, had a pathological tubal factor, unimpaired ovarian function, and male partners with a normal spermiogram. They postulated that a

reduced quality of the oocytes due to smoking may be compensated by a morphologically and functionally intact spermatocyte. The cutoff they used to distinguish active smokers from nonsmokers and passive smokers (> 50 ng/mL) is higher than the currently accepted cutoff (< 10 or 15 ng/mL) for serum cotinine. Therefore, some of the women they designated as nonsmokers may have had passive smoke exposure. However, they still did not see a difference in fertilization and pregnancy rates between active smokers and nonsmokers. IVF does not mimic natural conception, and this is a serious limitation of this study in terms of generalizing the results.

Chung et al., 1997. This study investigated the effects of active and passive smoking on the reproductive outcomes of patients undergoing gamete intrafallopian transfer (GIFT) because of infertility. In this procedure oocytes are retrieved through the vagina, mixed with sperm, and transferred into each fallopian tube with a catheter in a laporoscopic procedure. A total of 98 women who underwent their first GIFT procedures at the University of South Florida from April 1991 to December 1994 were included in the study. GIFT was performed on patients who had at least one normal patent fallopian tube and absence of a "severe male factor" (not explained by authors). After ovarian stimulation with gonadotropin-releasing hormone agonist and hMG, transvaginal oocyte retrieval was performed and laporoscopic GIFT was begun. In this procedure two or three retrieved oocytes mixed with 100,000 washed sperm are transferred into each gently elevated and straightened fallopian tube with a catheter.

A detailed smoking history, including duration and amount of smoking, was obtained from chart review and an additional telephone survey. Passive smokers were patients who had at least one household member (e.g., husband) who smoked. There were 66 nonsmokers, 19 smokers and 13 passive smokers. The authors also looked at possibly confounding variables such as age, diagnosis (unexplained infertility, endometriosis, anovulation, slight male factor, corrected tubal factor or cervical factor), levels of estradiol, total amount of hMG required and number of oocytes transferred. They did not control for these variables in the analysis, but they compared nonsmokers, active smokers and passive smokers with respect to these variables. Active smokers had a higher incidence of anovulation as compared to nonsmokers and passive smokers, and they required a significantly higher amount of hMG for controlled ovarian stimulation (COH). No statistically significant difference was found in the other

variables between the groups. The analysis of the pregnancy data was done using a chi-square test of the unadjusted difference in proportions. Active and passive smokers were compared individually to nonsmokers. Pregnancy and live birth rates for active smokers (15.8% and 10.5%, respectively) were significantly lower than those for passive smokers (46.2% and 23.1%) and nonsmokers (45.5% and 33.3%). The authors stated that no difference was noted between the latter two groups. However, there were few passive smokers and the ability to detect a statistically significant difference may have been limited. The observed differences between active smokers and passive or nonsmokers in pregnancy and live birth rates could be caused by a decreased fertilization rate, abnormal tubal transport or decreased implantation rate in smokers.

Jensen et al., 1998. This was a prospective study investigating the effects of active smoking and exposure *in utero* and during childhood to tobacco smoke on fecundability in 430 Danish couples recruited during 1992 to 1995. Recruitment occurred via a nationwide mailing of a letter to 52,255 trade union members (metalworkers, office workers, nurses, and day-care workers) who were 20-35 years old, lived with a partner, and had no children. The couples were enrolled into the study when they discontinued birth control and were followed for six menstrual cycles or until a clinically recognized pregnancy occurred. Both partners completed a questionnaire on demographic, medical, reproductive and lifestyle factors at enrollment and reported changes in occupational exposures and lifestyle factors (including smoking habits) in a monthly questionnaire. Smoking habits were reported as the number of cigarettes, cigars, or pipes smoked per day. Exposure to tobacco smoke *in utero* was ascertained by asking each partner "Did your mother smoke when she was pregnant with you." The men provided a semen sample at enrollment and once during the menstrual period of each cycle. Unlike the women in the Hull (2000) study, who did not report coital frequency, the women in this study recorded sexual intercourse daily. If couples had no intercourse from day 11 to 20 in the cycle, the cycle was excluded from analysis.

The authors used survival analysis to determine the cycle-specific association between smoking exposure and fecundability. This was equivalent to logistic regression on the total number of observed cycles with the outcome "pregnant/not pregnant." They constructed three dummy variables for smoking exposure: current exposure, exposure *in utero*, and exposure to

both. The reference group was no current smoking or exposure *in utero*. Since passive smoking during childhood was not associated with fecundability in bivariate analyses, this exposure was not included in the final models. They examined several potential confounders and excluded those that changed the association between the smoking variable and fecundability by less than 10% after exclusion. They performed separate models for women and their partners. The model with male smoking included female smoking but did not include semen quality because this may have masked an effect of male smoking on fecundability.

After adjustment for female body mass index and alcohol intake, diseases in female reproductive organs, semen quality, and duration of the menstrual cycle, the fecundability odds ratio for smoking women who were also exposed to tobacco smoke *in utero* was 0.53 (95% CI 0.31-0.91) compared with unexposed nonsmokers. Fecundability odds ratio for nonsmoking women exposed *in utero* was 0.70 (95% CI 0.48-1.03) and that for female smokers not exposed *in utero* was 0.67 (95% CI 0.42-1.06). If a woman stopped smoking within a year prior to the attempt to conceive, her fecundability odds ratio was similar to the women who never smoked (1.06, 95% CI 0.63-1.81). Exposure *in utero* was also associated with a decreased fecundability in nonsmoking males (OR = 0.68, 95% CI 0.48-0.97). However, present smoking in males did not reduce fecundability significantly.

This study had several strengths, including its prospective design. This allowed the authors to investigate the effects of tobacco exposure on women whose fertility was undetermined at the start of the study, unlike retrospective studies of women who have become pregnant. In addition, detailed exposure information was collected as soon as the women began trying and in each cycle prior to the knowledge of the outcome of the cycle, reducing recall bias and obtaining more accurate measures of exposure. Data on sperm parameters and coital frequency were collected in this study, unlike the other studies of fecundability and exposure to tobacco smoke. Cycles where no intercourse occurred during the period of ovulation were excluded, thus eliminating a possible source of bias. Finally, the authors carefully examined and controlled for a variety of potentially confounding variables. However, excluding semen quality from the confounders included in the adjusted analyses of male fecundability may have affected the validity of those analyses because semen quality could certainly have been a factor

independent of the effect of smoking. An analysis stratified by semen quality (good vs poor) was not performed.

Hull et al. (2000) studied pregnant women enrolled in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) in the United Kingdom whose date of expected delivery was between April 1, 1991 and December 31, 1992. To be eligible for the study a pregnancy had to reach 24 weeks. All cases in which the woman's partner was not the father of the child were excluded from analysis. Analysis was limited to women who had conceived intentionally (n=8,559). The authors studied fecundability (the probability of conceiving in a given menstrual cycle) by measuring time to conception in these women. Time to conception was categorized as < 6 months, 6-11 months, 1-3 years, or > 3 years. Several measures of exposure to tobacco smoke at the time when conception was being attempted were ascertained from a questionnaire: amount of active smoking of the woman; amount of active smoking of her partner, as reported by the partner; and the woman's exposure to environmental tobacco smoke from her partner, other household members, or at work. The authors did not collect data on the actual amount of cigarette smoke exposure from other household members or at work.

The authors also collected information on a large number of potentially confounding variables including number of previous pregnancies; number of previous live births; ages of the mother and her partner at conception; their ethnic origins; highest education level of the mother and her partner; duration of oral contraception use; mother's and her partner's alcohol consumption; home ownership status; housing type; crowding at home (number of persons per room); years of cohabitation; and, before pregnancy, the woman's body mass index (BMI). They performed a stepwise regression to determine which of these variables to include in an adjusted logistic regression model of the smoking and passive smoking variables for two outcomes (conception beyond 6 or 12 months of trying).

After controlling for confounding factors, delayed conception was statistically significantly associated with both active smoking by the woman and by her partner and with passive smoking by the woman (including active smoking by her partner). Passive smoking was not evaluated in the partners. For active smoking by both the mother and her partner there appeared to be a trend in the number of cigarettes smoked and increased odds of taking longer

than 6 or 12 months to conceive. In the mother the adjusted odds ratio for taking longer than 6 months to conceive increased from 1.22 (95% CI, 0.92-1.62) for 1-4 cigarettes per day to 1.59 (95% CI, 1.28-1.99) for $\geq$ 20 cigarettes per day compared with no active smoking (but women with passive exposure were included in the reference group). A similar trend was seen for smoking by the father and conception by 6 months, and the overall effect of smoking was statistically significant.

The authors also analyzed the woman's exposure to active and passive smoking using nonsmokers not exposed to tobacco smoke as the reference group. In this analysis the adjusted odds ratio for only active smoking (all levels of smoking combined) was 1.23 (95% CI, 0.98-1.49) for conception after 6 months and 1.54 (95% CI, 1.19-2.01) for conception after 12 months. For passive only exposure these odds ratios were, respectively, 1.17 (95% CI, 1.02-1.37) and 1.14 (95% CI, 0.92-1.42). Finally, for both active and passive smoke exposure these adjusted odds ratios increased to 1.51 (95% CI, 1.27-1.78) and 1.57 (95% CI, 1.26-1.96), for conception after 6 months and after 12 months, respectively. The authors also looked at exposure to passive smoke separately at home and at work and found an equally strong effect in both. However, statistical significance was lost when the subgroups were analyzed separately.

This study confirmed the established observation of reduced fertility in women who smoke cigarettes and provided new evidence of delayed conception if the man smokes or the woman is exposed to passive smoking at home or at work. The authors stated that "the fact that a woman's exposure to her partner's smoking did not exert a greater effect than exposure to smoking at work suggests a real effect of passive smoking on the woman that was not confounded by the likely effect of her partner's smoking on his sperm quality." The strengths of this study include very large sample size, detailed information on active and passive smoking and control of several important confounding variables. Limitations of this study include its restriction to one geographic area and its retrospective design. Also there were no data on coital frequency. However, recollection of time to conception has been found to be reliable, and information was collected early in pregnancy. The effect of smoke exposure may be a critical factor in women attempting to conceive in later life or those who require treatment for distinct subfertility.

5.1.3. Animal Studies of Female Fertility and Fecundability and Tobacco Smoke Exposure

The standard study design for evaluating male and female reproductive toxicity, the multi-generation breeding study, had not apparently been conducted with tobacco smoke before the 1997 report. However, more recently Florek and Marszalek (1999) studied the influence of exposure to tobacco smoke on mating, fecundity and fertility in rats. They found that the mating index and the fertility index (number of females giving birth/number of mating females) decreased with increasing concentrations of carbon monoxide in the cigarette smoke. However, the fecundity index (number of pregnant females/number of females with evidence of mating) actually increased with increasing exposure. Although trends were present, none of the differences were reported to be statistically significant. However, the authors did not conduct a test for trend in their results.

Two studies of ovarian cyclicity in female rats using mainstream smoke have been reported. Tachi and Aoyama (1983; 1988) found disrupted estrus cycles but no effect on ovulation (number of corpora lutea produced once estrus occurred) or mating behavior (once estrus occurred) with inhalation exposure to mainstream smoke. McLean *et al.* (1977) found that mainstream smoke exposure in rats delayed the luteinizing hormone surge associated with ovulation. In this study, the incidence of ovulation was reduced in rats exposed to smoke from a high (but not a low) nicotine cigarette. No studies of ovarian cyclicity using sidestream smoke have been reported.

5.1.4. Discussion and Conclusions

The human studies published since the 1997 OEHHA report continue to support the association of active smoking in the woman with reduced fertility and fecundability. However, the association with ETS is less clear. Most of the studies used smoking in the male partner as the measure of passive exposure in the woman and did not ascertain number of cigarettes smoked by the male or other measures of possible ETS exposure. Only Hull *et al.* (2000) collected information on number of cigarettes smoked per day by the male partner. After controlling for several confounders they did find a statistically significant delay to conception if the father smoked, and there was a trend of increasing odds ratios with increasing number of cigarettes smoked per day. These authors also found an effect of exposure to smoke at work by the

woman, but the number of women so exposed was too small for this to be statistically significant. The main weakness of that very large study (n=8,559) was that they failed to collect information on frequency of sexual intercourse. In the Bolumar (1996) study smokers in Spain and Italy had less frequent sexual intercourse, while the opposite was true in the Danish and German samples. Thus, coital frequency may have confounded the relationship between ETS exposure and delay to conception. The rest of the studies, which recorded yes/no for male smoking, failed to find a statistically significant delay to conception or reduced fecundability ratio with male smoking. In the Jensen (1998) study present smoking in the husbands reduced the fecundity ratio to 0.83, but this was not statistically significant. However, exposure to tobacco smoke *in utero* in nonsmoking husbands was associated with a statistically significant reduction in fecundity in that study. There was also a similar, almost statistically significant, reduction in fecundity for nonsmoking women exposed to tobacco smoke *in utero*.

In conclusion, there is suggestive evidence of an association of ETS exposure with effects on female fertility and fecundability. Large, carefully designed studies, including more quantitative measures of ETS exposure, are needed to conclusively verify these effects.

5.2. Other Female Reproductive Effects

In addition to studies of fertility and fecundability, investigators have examined the role of exposure to tobacco smoke on earlier age at menopause and on rates of menstrual disorders.

5.2.1. Overview of Human Studies of Other Female Reproductive Effects and Active Smoking

Substantial data exist to document that smokers have earlier age at menopause (U.S. DHHS, 1980; Midgette and Baron, 1990; Tajtakova *et al.*, 1990). The mean age at menopause in smokers is on average two years less than that of nonsmokers. This reduction may be due in part to the anti-estrogenic effect of active smoking (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986). Some studies have also suggested increases in menstrual disorders associated with cigarette smoking (Brown *et al.*, 1988; Sloss and Frerichs, 1983).

5.2.2. Human Studies of Other Female Reproductive Effects and ETS Exposure: Summary of previous findings

In its 1997 report, OEHHA reviewed two studies examining the effects of passive smoking on age at menopause. Everson *et al.* (1986) reported an association of ETS exposure and lower age at menopause. Data were obtained from 261 women who had been controls in a case-control study of cancer. The mean age at menopause was reduced by 2 years among nonsmoking women whose spouses smoked, compared to those whose spouses did not smoke. Whether the decrease of 2 years in the age at menopause was statistically significant was not discussed. After adjusting for some confounders (age, race, education, and alcohol intake) the risk of "early menopause", which was not defined, was elevated in nonsmokers exposed to ETS compared to those not exposed (OR=2.1, 95% CI = 1.04-4.5). The authors found that childhood exposure to maternal, but not paternal smoking was associated with early menopause. However, only four subjects had mothers who smoked, so the estimate (OR) of the maternal association was probably imprecise. The other study (Tajtakova *et al.*, 1990) provided data on age at menopause and exposure to ETS, but it was published in Slovak. According to the English abstract, those exposed to ETS had a mean age at menopause that was slightly younger than nonexposed nonsmokers. A difference of -0.7 years (95% CI = -1.9-0.51) was calculated from data presented in a table. This difference was unadjusted for confounders.

5.2.3. Human Studies of Other Female Reproductive Effects and ETS Exposure: Newer Epidemiologic Data

Table 5.2 ETS exposure and other female reproductive effects

Authors (yr) Location	Design (study size)	Exposure Definition/Measure	Results	Comments
Cooper *et al.* (1995) North Carolina	Cross-sectional study of follicle stimulating hormone (FSH) (n=290)	Smoking by any household member and *in -utero* exposure[1]	FSH concentrations 66% (27%-116%) higher among current smokers (Mean FSH 14.0 mIU/mL), and 39% (4%-86%) higher among nonsmokers with passive exposure (11.7 mIU/mL) compared to nonsmokers without passive exposure (8.4 mIU/mL). *In-utero* exposure was not related to FSH levels.	Controlled for age, body mass index, dietary galactose consumption. Evaluated other variables not found to be confounders. Women were ages 38 to 49 years.
Hornsby *et al.* (1998) Illinois	Prospective study of menstrual function using a daily menstrual diary for 6 months (n=358)	Living with or sharing a workplace with a smoker.	Mean duration of menses 5.8 days in nonsmokers and 5.5 days for passive exposure. Duration of dysmenorrhea (painful menses) 2.0 days for nonsmokers and 2.6 days for passive exposure. P values for trend test (including 2 active smoking categories) = 0.01 for duration of menses and 0.003 for duration of dysmenorrhea.	Controlled for exercise, body mass index, caffeine index, alcohol use history of tubal ligation , stress and duration of menses.
Cooper *et al.* (1999) Minnesota	Prospectively collected data on age at menopause. Retrospective smoking information (n=543)	Living with a smoker.	Mean age at menopause 0.6 (-0.2-1.4) years higher for never smokers with passive exposure vs. never smokers without passive exposure.	Only 62% of original cohort of college students recorded menstrual data for 5 or more years.
Chen *et al.* (2000) China	Prospective study of dysmenorrhea in newlywed, nulliparous nonsmokers (n=165)	Average cigarettes smoked per day by regular household member.	Adjusted ORs of dysmenorrhea for tertiles of exposure Low: 1.1 (0.5-2.6), Medium: 2.5 (0.9-6.7) High: 3.1 (1.2-8.3).	Adjusted for district, body mass index, education, passive smoking at work, and several other work exposures.

[1] *In -utero* exposure indicates that the mother of the target participant smoked during her pregnancy.

Cooper et al., 1995. This cross-sectional study examined the effects of several forms of tobacco exposure on ovarian status, as reflected by early follicular phase follicle stimulating hormone (FSH) levels in serum. A high serum level of FSH is a recognized clinical index of menopausal status and significant increases in FSH occur before menstrual cycles cease. Study subjects, 290 highly educated women ages 38-49 years, who had not had a hysterectomy or oophorectomy, were recruited through posters and advertisements in Durham and Orange Counties, North Carolina. FSH levels were measured in blood drawn from each participant on the second, third or fourth day of the menstrual cycle or at her earliest convenience if she had not menstruated in the past two months. Active smoking was defined as having smoked at least one cigarette per day for at least 3 months of the year, and passive smoking was defined as currently living with anyone who regularly smokes cigarettes at home. Prenatal exposure was assessed by asking whether the mother had smoked regularly while pregnant with the participant or the father had smoked regularly at home during this time.

The authors created a smoking status variable with three categories: current smokers (smoked during the past two years, n=31), nonsmokers (never- and ex-smokers) with passive exposure (n=25), and nonsmokers without passive exposure (n=232, the reference group). After controlling for age, body mass index, and dietary galactose consumption, the geometric mean FSH was 14.0 mIU/mL in current smokers, 11.7 mIU/mL in nonsmokers with passive smoke exposure and 8.4 mIU/mL in the reference group. These differences were statistically significant ($p < 0.05$). Other variables such as race, education, parity and caffeine consumption were evaluated and found not to be confounders in the analysis. The authors stated that similar results were seen when current hormone use was in the analysis, and the passive smoke effect was seen even when the analysis was limited to women who had never smoked. They also stated that prenatal exposure to smoking was not related to FSH levels, and no effect of ex-smoking was seen in this study. These data were not presented in the paper.

Hornsby et al. (1998) studied menstrual function in 358 women 37-39 years old whose mothers had participated, while pregnant with them, in a randomized clinical trial of diethylstilbestrol (DES) from 1950 to 1952. The women, who were traced and

interviewed in 1990, were eligible for study if they were still menstruating and not taking exogenous hormones or other medication known to affect menses. Study participants were asked to keep a daily menstrual diary for 6 months. Smoking exposure was categorized as none (N=211), passive (nonsmokers who reported living or sharing a workplace with a smoker, N=64), light (up to ½ pack per day, N=35), or moderate/heavy (greater than ½ pack per day, N=48)). Prenatal exposure to DES was equally distributed in smokers and nonsmokers. Menstrual endpoints included cycle length (days), duration of menstrual bleeding (days), daily amount of bleeding (based on a subjective score from 1 = spotting to 4 = heavy), and dysmenorrhea (days of premenstrual and/or menstrual pain). For each of these endpoints, a mean was generated for each woman, and means of these means were then compared across smoking categories. The means were adjusted for potentially confounding variables that altered the coefficient for smoking by 10% or greater. These variables included exercise, body mass index, caffeine index, alcohol use, history of tubal ligation, stress and duration of menses.

The authors found that active smoking was associated with decreased duration of bleeding, increased daily amount of bleeding, and increased duration of dysmenorrhea. The duration of bleeding was also reduced in women with passive smoke exposure compared with nonsmokers. After adjusting for a history of tubal ligation, the mean duration of menses was 5.8 days in nonsmokers and 5.5 days in women with passive smoke exposure. In addition, the mean duration of dysmenorrhea, adjusted for exercise, stress and duration of menses, in women with passive smoke exposure was 2.6 days compared with 2.0 days for nonsmokers. Both these differences were statistically significant in the exposure trend test which included all categories of smoke exposure ($p=0.01$ and $p=0.003$, respectively).

Cooper et al. (1999) studied active and passive smoking and the occurrence of natural menopause among female college students who enrolled in a reproductive health study in Minnesota between 1934 and 1939 and recorded menstrual data for 5 or more years while in their 20's. In 1990-1991 943 of these women were successfully located. A total of 716 self- respondents and 158 proxy respondents (most often husband, daughter or other relative) completed a questionnaire which included active smoking status (yes/no) for

each age between 10 and 79 years and cigarettes per day by decade. Passive smoking was defined as living with a smoker, and women were placed into categories of no adult passive smoking, passive exposure only more than 5 years before menopause and passive exposure within the 5 years before menopause. The analysis was limited to 543 women who had undergone natural menopause (i.e not surgically or medically induced). As has been reported in previous studies the authors found a decrease in age at menopause of 0.8 years (-0.8, 95% CL = -1.5, -0.0 years) among current smokers compared to never smokers [note reference group includes 362 never active, but those include 117 with passive smoking]. Adjusting for body mass index at age 30 did not substantially change the results. The authors did not find a lower age at menopause with passive smoke exposure. The mean age at menopause among the 117 never-smokers with passive smoke exposure was 0.6 years higher (95% confidence limits = -0.2, 1.4) compared with the 198 never-smokers without passive smoke exposure. These results are not in agreement with the Everson *et al.* (1986) paper described above, which found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. However, there were only a total of 261 women in that study, so that estimate was probably imprecise. The strength of Cooper *et al.* (1999) is that it included prospectively collected data on age at menopause and a high response rate among women who recorded menstrual data for 5 or more years (1,134 of the 1,807 college students who entered the cohort in 1934-1939). However, there may have been some selection bias because only 62% of the original cohort recorded menstrual data for 5 or more years. If those women who recorded this data were healthier than those who did not, this could have reduced the difference in age at menopause between smokers and nonsmokers. Although 51% of the women in the analysis worked outside the home during ages 40-44, workplace exposure to passive smoke was not included.

Chen et al. (2000) conducted a prospective study of the effects of environmental tobacco smoke on dysmenorrhea in 165 women living in two districts of Shenyang, China. The women were part of an established cohort of newly wed couples recruited to participate in a comprehensive study of the effects of various environmental and occupational exposures on reproductive outcomes. Women with a history of dysmenorrhea were

excluded from the study in order to examine the effects of ETS on the incidence of dysmenorrhea. This study had unique advantages over previous studies of menstrual dysfunction. In China, few women smoke cigarettes, but exposure to ETS is high because of the high prevalence of smoking among men. Parity is suggested to be associated with menstrual pain (nulliparous women have a higher prevalence of dysmenorrhea than multiparous women). In this study all the subjects were newly wed, nulliparous, nonsmokers who intended to conceive and thus used no contraceptives during the follow-up period. They completed daily diaries on menstrual bleeding and associated symptoms, exposure to tobacco smoke and other occupational exposures and were followed up until the occurrence of clinical pregnancy or up to 1 year. Dysmenorrhea was defined as 2 or more days of menstrual pain (abdominal or low back pain) during menstrual bleeding. For each menstrual cycle, ETS exposure at home was characterized by the average number of cigarettes smoked per day by regular household members indoors while the subject was present; four ETS subgroups were formed: no exposure and low, medium and high tertiles of exposure. Occupational exposure to ETS was recorded as a yes/no variable.

The 165 women contributed a total of 625 prospectively followed menstrual cycles. ETS exposure was reported in 77% of the cycles. The crude incidence rate of dysmenorrhea in these cycles was 9.7% for the unexposed and 9.4%, 13.8% and 16.9% respectively for the low, medium and high tertiles of ETS exposure. This dose response was also seen when the incidence of dysmenorrhea was adjusted for district, body mass index, education, occupation, area of residence, shift work, perceived stress, occupational exposure to chemical hazards, noise and dust, passive smoking at work, and season (adjusted odds ratios for low, medium and high tertiles of ETS exposure were 1.1 (95% confidence interval (CI), 0.5-2.6), 2.5 (95% CI, 0.9-6.7) and 3.1 (95% CI, 1.2-8.3), respectively . Generalized estimating equations were used to account for multiple cycles per woman. In this study the authors found a significant dose-response even though the levels of passive smoking were not particularly high. The average daily exposures per cycle ranged from 0.02 to 10.3 cigarettes. The “middle” tertile was 0.8 to 2.5 cigarettes per day.

5.2.4. Discussion and Conclusions

The one new study of age at menopause and ETS exposure failed to find a lower age at menopause in women exposed to ETS from living with a smoker. These results are not in agreement with the Everson *et al.* (1986) paper, which found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. Neither paper recorded cigarettes smoked per day by the spouses or workplace exposure to ETS. A study of women ages 38 to 49 years did find higher FSH levels in current smokers and nonsmokers with passive exposure compared to nonsmokers without passive exposure after controlling for age, body mass index and dietary galactose consumption (Cooper *et al.*, 1995). This may indicate an effect on ovarian function, and increased FSH level is a clinical indication of peri-menopause. Other evidence from studies in active smokers demonstrates that cigarette smoke is anti-estrogenic (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986); this would provide a plausible basis for earlier menopause in women exposed to cigarette smoke.

Two recent studies found an effect of ETS on dysmenorrhea (Chen *et al.*, 2000; Hornsby *et al.*, 1998). The Chen study actually found a dose response for tertiles of cigarettes smoked per day by a household member in a cohort of Chinese women who were nonsmokers. Both studies controlled for potential confounders such as body mass index.

There continues to be inconsistency in results and very few studies evaluating the effect of ETS exposure on female reproductive function other than fecundity and fertility. There is, however, suggestive evidence of biochemical effects of ETS on measures that affect age at menopause and female reproductive organ health, as well as suggestive evidence of dysmenorrhea from exposure to ETS.

5.3. Male Reproductive Toxicity

Male reproductive toxicity includes altered sperm parameters, such as lower density, decreased motility or abnormal morphology, and effects on fertility.

5.3.1. Overview of Human Studies of Male Reproductive Toxicity and Active Smoking

The following review is from the 1997 OEHHA report. "Several studies have shown an association between active smoking and altered sperm parameters, including abnormally shaped sperm (Evans *et al.*, 1981), decreased seminal fluid and decreased sperm motility (Marshburn *et al.*, 1989). Authors of a recent meta-analysis of the literature on sperm density and smoking (Vine *et al.*, 1994) concluded that smokers' sperm density is on average 13-17% lower than that of nonsmokers. The 1980 Surgeon General's Report (U.S. DHHS, 1980) stated, "spermatogenesis, sperm morphology, sperm motility and androgen secretion appear to be altered in men who smoke". These outcomes could result from some of the same mechanisms proposed to explain the effects of smoking on female reproductive functions, namely alterations in hormone regulation and gamete production."

5.3.2. Human Studies of Male Reproductive Toxicity and Exposure to ETS

5.3.2.1. Summary of previous findings

The following is the summary of the findings for male reproductive toxicity from the 1997 report:

"No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. A study which examined the effects of early exposure to maternal smoking (both in utero and postnatal ETS exposure) found significant differences in sperm motility and oligospermia in the subgroup of subjects not exposed to DES. Associations have been seen in human studies of active smoking and sperm parameters. Therefore, the findings of sub-fecundability in women exposed to ETS by husbands who smoke may in fact be due to direct effects of active smoking on male reproductive capacity, rather than to the effects of ETS exposure of the women.

In conclusion, due to the paucity of data it is not possible to determine whether there is a causal association between ETS exposure and male reproductive dysfunction."

5.3.2.2. Newer Epidemiologic Data

No published studies were found that were designed to examine the association between ETS exposure of males and altered sperm parameters or fertility. However, evidence that the male reproductive system is affected by passive smoking was provided by Pacifici *et al.* (1995), who found that exposure to ETS in nonsmokers results in measurable nicotine and cotinine levels in seminal plasma. Furthermore, seminal plasma cotinine concentration showed a significant positive correlation with degree of reported exposure. An in-vitro study of the effects of nicotine and cotinine on motility of sperm from nonsmokers usually not exposed to passive smoking (Gandini *et al.*, 1997) found that nicotine and cotinine at the average levels found in smokers' seminal plasma did not affect sperm motility, while a second experiment using aspirated cigarette smoke demonstrated a sharp reduction in all the sperm kinetic parameters. This study suggests that constituents of tobacco smoke other than nicotine or cotinine are responsible for the effects on semen quality.

The study by Jensen *et al.* (1998) described above in section 5.2.2.2 found that exposure to tobacco smoke in utero was also associated with a statistically significant decreased fecundability odds ratio in males (0.68, 95% CI 0.48-0.97). The other studies reported above in Section 5.2.2.2 did not collect information on passive smoking in the male partners.

5.3.3. Discussion and conclusions

There is only one new study that examined the effect of ETS exposure on reproductive dysfunction in males as part of a study of fecundity in couples. In this study exposure to tobacco smoke in utero was the measure of passive exposure for males. Further studies are needed which look at exposure to passive smoke outside of the home in nonsmoking males. Due to the paucity of data it is not possible to determine whether there is an association between ETS exposure and male reproductive dysfunction.

5.4. References

Baird DD, Wilcox AJ (1985). Cigarette smoking associated with delayed conception. JAMA 253(20):2979-83.

Bolumar F, Olsen J, Boldsen J (1996). Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. The European Study Group on Infertility and Subfecundity. Am J Epidemiol 143(6):578-87.

Brown S, Vessey M, Stratton I (1988). The influence of method of contraception and cigarette smoking on menstrual patterns. Br J Obstet Gynaecol 95(9):905-10.

Chen C, Cho SI, Damokosh AI, Chen D, Li G, Wang X, Xu X (2000). Prospective study of exposure to environmental tobacco smoke and dysmenorrhea. Environ Health Perspect 108(11):1019-22.

Chung PH, Yeko TR, Mayer JC, Clark B, Welden SW, Maroulis GB (1997). Gamete intrafallopian transfer. Does smoking play a role? J Reprod Med 42(2):65-70.

Cooper GS, Baird DD, Hulka BS, Weinberg CR, Savitz DA, Hughes CLJ (1995). Follicle-stimulating hormone concentrations in relation to active and passive smoking. Obstet Gynecol 85(3):407-11.

Cooper GS, Sandler DP, Bohlig M (1999). Active and passive smoking and the occurrence of natural menopause. Epidemiology 10(6):771-3.

Daling JR, Weiss N, Spadoni L, Moore DE, Voigt L (1986). Cigarette smoking and primary tubal infertility. Rosenberg M, (Editor). In: Smoking and Reproductive Health . Littleton, MA: PSG Publishers.

Evans HJ, Fletcher J, Torrance M, Hargreave TB (1981). Sperm abnormalities and cigarette smoking. Lancet 1(8221):627-9.

Everson RB, Sandler DP, Wilcox AJ, Schreinemachers D, Shore DL, Weinberg C (1986). Effect of passive exposure to smoking on age at natural menopause. Br Med J 293(6550):792.

Florack EI, Zielhuis GA, Rolland R (1994). Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. Prev Med 23(2):175-80.

Florek E, Marszalek A (1999). An experimental study of the influences of tobacco smoke on fertility and reproduction. Hum Exp Toxicol 18(4):272-8.

Gandini L, Lombardo F, Lenzi A, Culasso F, Pacifici R, Zuccaro P, Dondero F (1997). The in-vitro effects of nicotine and cotinine on sperm motility. Hum Reprod 12(4):727-33.

Grab D, Lucke R, Benz R, Wenderlein M (1988). [The significance of passive smoking in pregnancy]. Z Geburtshilfe Perinatol 192(3):126-9.

Hornsby PP, Wilcox AJ, Weinberg CR (1998). Cigarette smoking and disturbance of menstrual function. Epidemiology 9(2):193-8.

Howe G, Westhoff C, Vessey M, Yeates D (1985). Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. Br Med J 290(6483):1697-700.

Hull MG, North K, Taylor H, Farrow A, Ford WC (2000). Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. Fertil Steril 74(4):725-33.

Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, Ernst E, Bonde JP, Skakkebaek NE, Olsen J (1998). Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. Am J Epidemiol 148(10):992-7.

MacMahon B, Trichopoulos D, Cole P, Brown J (1982). Cigarette smoking and urinary estrogens. N Engl J Med 307(17):1062-5.

Marshburn PB, Sloan CS, Hammond MG (1989). Semen quality and association with coffee drinking, cigarette smoking, and ethanol consumption. Fertil Steril 52(1):162-5.

McLean BK, Rubel A, Nikitovitch-Winer MB (1977). The differential effects of exposure to tobacco smoke on the secretion of luteinizing hormone and prolactin in the proestrous rat. Endocrinology 100(6):1566-70.

Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J (1986). Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. N Engl J Med 315(21):1305-9.

Midgette AS, Baron JA (1990). Cigarette smoking and the risk of natural menopause. Epidemiology 1(6):474-80.

National Cancer Institute (1999). Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency. Smoking and Tobacco Control Monograph no. 10. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institite, NIH Pub. No 99-4645.

Olsen J (1991). Cigarette smoking, tea and coffee drinking, and subfecundity. Am J Epidemiol 133(7):734-9.

Pacifici R, Altieri I, Gandini L, Lenzi A, Passa AR, Pichini S, Rosa M, Zuccaro P, Dondero F (1995). Environmental tobacco smoke: nicotine and cotinine concentration in semen. Environ Res 68(1):69-72.

Schwingl PJ (1992). Prenatal smoking exposure in relation to female adult fecundability [United Microfilms International]. Ann Arbor, MI.

Sloss EM, Frerichs RR (1983). Smoking and menstrual disorders. Int J Epidemiol 12(1):107-9.

Spira A , Mousan J , Schwartz S (1987). Smoking and fecundity. Rosenberg MJ, (Editor). In: Smoking and Reproductive Health. Littleton, MA: PSG Publishing Company.

Sterzik K, Strehler E, De Santo M, Trumpp N, Abt M, Rosenbusch B, Schneider A (1996). Influence of smoking on fertility in women attending an in vitro fertilization program. Fertil Steril 65(4):810-4.

Stillman RJ, Rosenberg MJ, Sachs BP (1986). Smoking and reproduction. Fertil Steril 46(4):545-66.

Suonio S, Saarikoski S, Kauhanen O, Metsapelto A, Terho J, Vohlonen I (1990). Smoking does affect fecundity. Eur J Obstet Gynecol Reprod Biol 34(1-2):89-95.

Tachi N, Aoyama M (1983). Effect of cigarette smoke and carbon monoxide inhalation by gravid rats on the conceptus weight. Bull Environ Contam Toxicol 31(1):85-92.

Tachi N, Aoyama M (1988). Effects of cigarette smoke exposure on estrous cycles and mating behavior in female rats. Bull Environ Contam Toxicol 40(4):584-9.

Tajtakova M, Farkasova E, Klubertova M, Konradova I, Machovcakova L (1990). [The effect of smoking on menopause]. Vnitr Lek 36(7):649-53.

U.S. Department of Health and Human Services (1980). The Health Consequences of Smoking for Women: A Report of the Surgeon General. US Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.
.

Vine MF, Margolin BH, Morrison HI, Hulka BS (1994). Cigarette smoking and sperm density: a meta-analysis. Fertil Steril 61(1):35-43.

Weinberg CR, Wilcox AJ, Baird DD (1989). Reduced fecundability in women with prenatal exposure to cigarette smoking. Am J Epidemiol 129(5):1072-8.

Westhoff CI (1990). The epidemiology of infertility. Kiely M, (Editor). In: Reproductive and Perinatal Epidemiology. Boca Raton, FL: CRC Press, p. 43-61.

Wilcox AJ, Baird DD, Weinberg CR (1989). Do women with childhood exposure to cigarette smoking have increased fecundability? Am J Epidemiol 129(5):1079-83.